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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/954,771	10/20/97	INGRAM	P	HMV-006.11

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EXAMINER	
BRANNOCK, M	

ART UNIT	PAPER NUMBER
1646	26

DATE MAILED: 03/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/954,771	Ingham, PW
Examiner	**Group Art Unit**
Michael Brannock, Ph.D.	1646

☒ Responsive to communication(s) filed on *Jan 16, 2001*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 42-50, 69, 70, 76-86, 93, 96-100, 102-104, and 107-110* is/are pending in the applicat

Of the above, claim(s) *42-48, 78, and 79* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 49, 50, 69, 70, 76, 77, 80-86, 96-100, 102-104, and 107-110* is/are rejected.

☒ Claim(s) *93* is/are objected to.

☒ Claims *1, 42-50, 69, 70, 76-86, 93, 96-100, 102-104, and 107-110* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 18*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 21 8/1/01, have been entered in full.

2. Claims 1, 42-50, 69, 70, 76-86, 93, 96-100, 102-104, 107-110 are pending.

3. Claims 42-48, 78 and 79 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Further, claims 1, 49, 50, 69, 70, 76, 77, 80-86, 93, 96-100, 102-104 and 107-110 will be examined only to the extent that they read on *in vitro* methods of modulating neural cells with sonic hedgehog polypeptides, the requirement having been traversed in Paper No. 17, 311/00 and Paper No. 24, 1/16/01.

The traversal is on the grounds that a search of all the groups would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together:

(C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, Applicant argues that all of the inventions of the pending claims are classified in class 514, subclass 2 or 44, and that therefore it would not be an undue burden to search the pending claims. This argument has been fully considered but not deemed persuasive because these subsclasses encompass virtually all that is known in the art regarding the administration of polypeptides and polynucleotides. The separate inventions are each small parts of these classes, and although a search of any one of the groups may overlap that of another, the search of one group could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of any other group, and to search all groups would be burdensome. Additionally, in Paper No. 24, 1/16/01, Applicant submits that the election of species is being made for search purposes only. This statement is incorrect. As set forth in Paper 15, 12/20/99, the Sonic, Desert, and Indian Hedgehog polypeptides are each patentably distinct species, absent evidence to the contrary. Therefore, the restriction requirement is maintained and made FINAL.

Specification

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s), as well as the status of the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Sequence Rules Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: The specification makes reference to specific polynucleotide and polypeptide sequences; these references must contain a sequence identifier of the form: SEQ ID NO: X. See for example page 142. Applicants' help and cooperation is earnestly requested to identify any other sequences that may be present in the Application. Upon allowance, it is very likely that any such sequence not having the appropriate sequence identifier would be found and rejected by the printer. Appropriate correction is required.

Claim Objections

6. Claim 93 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot itself depend from a multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1, 49, 50, 69, 70, 76, 77, 80-86, 96-100, 102-104 and 107-110 provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common

subject matter, as follows: *in vitro* methods of promoting the growth, differentiation and/or survival of neuronal cells by contacting the cells with a sonic hedgehog protein.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 49, 50, 69, 70, 76-77, 80-86, 96-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons:

Claim 1 requires an effective amount of a hedgehog polypeptide, yet the claim does not require that the amount be effective at any particular thing, therefore it is unclear what additional limitations are put on the claim by the presence of the term "effective amount". It is suggested that the claim be re-worded such that the claim requires that the amount of the polypeptide be effective at promoting survival of neuronal cells, etc.

Claims which recite the term "hedgehog polypeptide" without reference to specific amino acid sequences are indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "hedgehog polypeptide". An artisan cannot determine what additional limitations are placed upon a claim by the presence of this term.

Claim 49 requires a method to increase the rate of survival of neuronal cells. The term "rate of survival" is confusing because it there is no art-recognized definition of the term and nor is there such a definition of the term provided in the specification. It is suggested that the phrase "increase the survival rate of the neuronal cells" would obviate this term.

Claim 77 requires a particular neural phenotype, *such as* a neuron or glia. The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 80 and 81 require "the effect of a naturally-occurring hedgehog protein". The claim is indefinite because the specification has not described the effect of a naturally-occurring hedgehog protein and nor is it known in the art what the effects of a naturally occurring hedgehog protein are. It is appreciated in the art that hedgehog proteins are enormously important in embryonic development and the effects of these proteins are extremely complex, and at present, the understanding of the particulars of the effects of hedgehog proteins is in its infancy. Therefore, the skilled artisan would not be able to unambiguously say what is and what is not "the effect of a naturally-occurring hedgehog protein".

Claim 83 requires that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim the applicant is seeking protection for. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes, see page 29 of the instant specification.

Claim 99 (line 3) requires a polypeptide encoded by at least a portion of a hedgehog gene of vertebrate origin corresponding to residues 64-567 of SEQ ID NO: 1. The phrase "corresponding to residues" is confusing because (a) the term residue is known in the art to refer to amino acids and not to nucleotides, and (b) it is unclear exactly how the portion is required to "correspond" to the residues.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 81 requires a hedgehog polypeptide that antagonizes the effects of a naturally occurring hedgehog polypeptide, yet the specification provides no teaching as to the identity of a polypeptide that has this property.

13. Claims 1, 49, 50, 69, 70, 76-77, 80, 82-86, 96-104 and 107-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13 or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass methods of promoting one or more of growth, differentiation and survival of adult neuronal cells in culture. The specification provides that neuronal cells grown in culture, including those from adult tissue, readily lose their differentiated state (see page 59,

line 18). Also, the specification puts forth that hedgehog proteins can be added to cultures of cells in order to maintain the integrity of a culture of terminally differentiated neuronal cells by preventing loss of differentiation (see page 59, lines 22-25). Additionally, the specification provides examples of the use of sonic hedgehog in the promotion of growth, differentiation, and survival of embryonic neuronal cells. It is known that sonic hedgehog is endogenously expressed in embryos, and one of skill in the art would therefore expect that embryonic tissues would be responsive to sonic hedgehog. However, the specification also discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Therefore, one of skill in the art would be required to perform undue trial and error experimentation in order to determine which of the multitude of adult neural cells is responsive to sonic hedgehog, if in fact any exist.

Additionally, the claims encompass an almost limitless number of polypeptides that comprise a portion of SEQ ID NO: 8, 11, 12, or 13, or comprise variants or portions of variants having a recited degree of identity to SEQ ID NO: 8, 11, 12, or 13. The specification sets forth that variants and portions can be used in the claimed methods, however, the specification does not provide sufficient guidance as to which of these variants and portions can actually be used to practice the claimed invention (see page 26 for example).

One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a polypeptide of SEQ ID NO: 8, 9, 12, or 13, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to promote neural cell growth, differentiation and/or survival. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

March 21, 2001

Daniel Romeo
Primary Examiner